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[From the Laboratory of Physiology in the Harvard Medical School]

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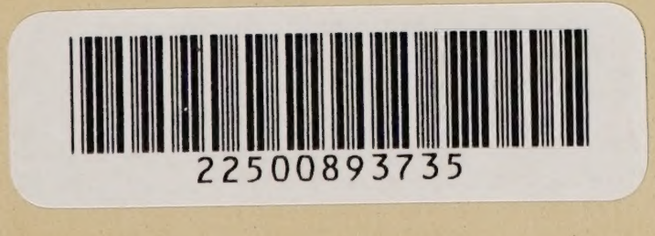

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THE EFFECT OF ADRENAL SECRETION ON MUSCULAR FATIGUE[1]

By W. B. CANNON and L. B. NICE
[*From the Laboratory of Physiology in the Harvard Medical School*]

IN the older literature on the adrenal glands the effect of their absence, or of injected extracts, on skeletal muscle was not unfrequently noted. As evidence accumulated, however, tending to prove that adrenal secretion has important relations with the sympathetic nervous system, its relations with skeletal muscle began to receive less consideration.

The muscular weakness of persons suffering from Addison's disease was well recognized before experimental work on the adrenals was begun. Experiments on rabbits were reported in 1892 by Albanese who showed that muscles stimulated after removal of the adrenal capsules, were much more exhausted than when stimulated the same length of time in the same animal before decapsulation.[2] Similarly Boinet reported that rats recently decapsulated were much more quickly exhausted in a revolving cage than were normal animals.[3]

More direct evidence of the effect of adrenal extract on skeletal muscle was brought forward by Oliver and Schäfer. After injecting the extract subcutaneously into a frog they found that the excised gastrocnemius muscle registered a curve of contraction about 33 per cent higher and about 66 per cent longer than the corresponding muscle not exposed to the action of the extract. Similar prolongation of the muscle curve was observed after injecting the extract intravenously into a dog.[4] A beneficial effect of adrenal extract on

[1] A preliminary report of this research was given at the meeting of the American Physiological Society, December, 1911. See Proceedings, this Journal, 1912, xxix, p. xxiv.

[2] Albanese: Archives italiennes de biologie, 1892, xvii, p. 243.

[3] Boinet: Comptes rendus, Société de Biologie, 1895, xlvii, pp. 273, 498.

[4] Oliver and Schäfer: Journal of physiology, 1895, xviii, p. 263. *See* also Radwánska, Anzeiger der Akademie, Krakau, 1910, pp. 728–736. Reviewed in Zentralblatt für Biochemie und Biophysik, 1911, xi, p. 467.

fatigued muscle, even when applied to the solution in which the isolated muscle was contracting, was claimed by Dessy and Grandis, who studied the phenomenon in a salamander.[5] Further evidence to the same conclusion was offered in a discriminating paper by Panella. He found that in heterothermic animals the active principle of the adrenal glands notably reinforced striated muscle, prolonging its ability to do work, and improving its contraction when fatigued. In homothermic animals the same effects were observed, but only after experimental procedures (anaesthesia, section of the bulb) had changed them to a condition resembling the heterothermic.[6]

The foregoing evidence indicates that decapsulation has a debilitating effect on muscular power, and that injection of extracts of the capsules has an invigorating effect. It seemed possible, therefore, that increased secretion of the adrenal glands, whether from direct stimulation of the splanchnic nerves or as a reflex result of pain or the major emotions, might act as a dynamogenic factor in the performance of muscular work. With this possibility the present investigation was concerned.

The Method

The general plan of the investigation consisted primarily in observing the effect of stimulating the splanchnic nerves, isolated from the spinal cord, on the contraction of a muscle whose nerve, also isolated from the spinal cord, was rhythmically and uniformly excited with break induction shocks. Thus only a blood connection existed between the splanchnic region and the muscle. Cats were used for most experiments, but results obtained with cats were confirmed on rabbits and dogs. To produce anaesthesia, in the cats and rabbits, and at the same time to avoid the fluctuating effects of ether, urethane (2 gm. per kilo body-weight) was given by a stomach-tube. The animals were fastened back-downward, over an electric warming pad, to an animal holder. Care was taken to maintain the body temperature at its normal level throughout each experiment.

The nerve-muscle preparation. — The muscle selected for record was usually the right *tibialis anticus*, though at times the right *extensor*

[5] Dessy and Grandis: Archives italiennes de biologie, 1904, xli, p. 231.

[6] Panella: Archives italiennes de biologie, 1907, xlviii, p. 462.

communis of the digits was employed. The anterior tibial nerve was bared for about two centimetres, severed proximally, and set in a Sherrington shielded electrode around which the skin was fastened by spring clips. By a small slit in the skin the tendon of the muscle was uncovered, and after being tightly ligatured with strong thread, was separated from its insertion. Thus a nerve-muscle preparation was made which was still connected with its proper blood supply. The preparation was firmly fixed to the animal holder by thongs looped around the hock and the foot, i.e., on either side of the slit through which the tendon emerged.

The ligature tied to the tendon was passed over a pulley and down to a pivoted steel bar which bore a writing point. Both the pulley and this steel writing lever were supported in a rigid tripod. In the earliest experiments the contracting muscle was made to lift weights (125 to 175 gm.), and was sometimes "loaded" with these weights; but in all the later observations the muscle pulled against a spring. In most instances the muscle was afterloaded, but by raising the muscle clamp the tension developed in the muscle at rest was made nearly equal to the pull of the spring at its shortest length. The "support," therefore, was little more than a constant base for relaxation. The pull of the spring as the muscle began to lift the lever away from the support was in most of the experiments 110 gm., with an increase of 10 gm. as the writing point was raised 4.5 mm. The magnification of the lever was 3.8.

The stimuli delivered to the anterior tibial nerve were, in most experiments, single break shocks of a value barely maximal when applied to the fresh preparation. The rate of stimulation varied between 60 and 300 per minute, but was uniform in any single observation. A rate which was found generally serviceable was 180 per minute. In a few experiments a regularly repeated tetanizing current was used.

Since the anterior tibial nerve contains fibres affecting blood-vessels, as well as motor fibres for skeletal muscle, the possibility had to be considered that stimuli applied to it might disturb the blood supply of the nerve-muscle preparation. Vasoconstriction would be likely to produce the most serious disturbance. The observations of Bowditch and Warren, that vasodilator rather than vasoconstrictor effects are produced by single induction shocks repeated at intervals

of not more than five per second,[7] reassured us as to the danger of diminishing the blood supply, for the rate of stimulation in our experiments never exceeded five per second and was usually two or three. Furthermore in using these different rates we have never noted any result which could reasonably be attributed to a diminished circulation.

The splanchnic preparation. — The splanchnic nerves were stimulated in various ways. At first only the left splanchnics in the abdomen were prepared. The nerves, separated from the spinal cord, were drawn into a Sherrington shielded electrode, which was attached by threads to the body wall. A rubber tube connected the electrode with the exterior of the body, and separated the wires from the abdominal viscera. The placing of this electrode, however, required so much time and, in spite of great care, was so likely to result in harmful pulling on the nerves, that some other device became necessary.

The form of electrode which was found most satisfactory was that

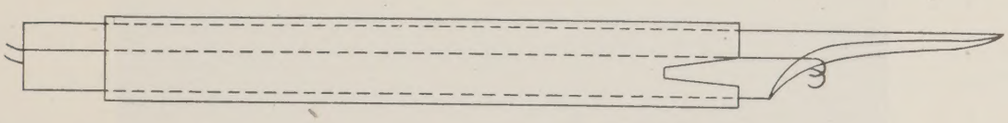


FIGURE 1. The shielded electrode used in splanchnic stimulation. For description see text.

illustrated in Fig. 1. It was made of a round rod of hard wood, bevelled to a point at one end, and grooved on the two sides. Into the grooves were pressed insulated wires ending in platinum hooks, which projected beyond the bevelled surface. Around the rod was placed a rubber tube which was cut out so as to leave the hooks uncovered when the tube was slipped downward.

In applying the electrode the left splanchnic nerves were first freed from their surroundings and tightly ligatured as central as possible. By means of strong compression the conductivity of the nerves was destroyed proximal to the ligature. The electrode was now fixed in place by thrusting the sharp end into the muscles of the back. This was so done as to bring the platinum hooks a few millimetres above the nerves. With a small seeker the nerves were next gently lifted over the hooks, and then the rubber tube was slipped downward until it came in contact with the body wall. Absorbent

[7] BOWDITCH and WARREN: Journal of physiology, 1886, vii, p. 438.

cotton was packed about the lower end of the electrode, to take up any fluid that might appear; and finally the belly wall was closed with spring clips. The rubber tube served to keep the platinum hooks from contact with the muscles of the back and the movable viscera, while still permitting access to the nerves which were to be stimulated. This stimulating apparatus could be quickly applied, and, once in place, needed no further attention.

In some of the latest experiments both splanchnic nerves were stimulated in the thorax. The rubber-covered electrode proved quite as serviceable there as in the abdomen.

The current delivered to the splanchnic nerves was a tetanizing current of such strength that no effects of spreading were noticeable.

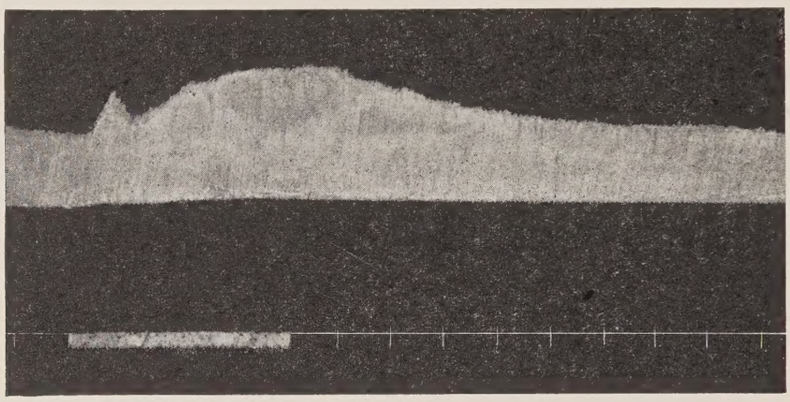


FIGURE 2. Upper record, contraction of the *tibialis anticus*, 80 times a minute, lifting a weight of 125 gm. Lower record, stimulation of the left splanchnic nerves, two minutes. Time, half minutes.

That splanchnic stimulation causes secretion of the adrenal glands has been proved in many different ways which need not be recounted here. On this assumption the present investigation was undertaken.

THE EFFECTS OF STIMULATING THE SPLANCHNIC NERVES

The effect on contraction of fatigued muscle, which can often be obtained by stimulating the left splanchnic nerves, is shown in Fig. 2. In this instance the muscle was afterloaded, and while contracting lifted a weight of 125 gm. The rate of stimulation was 80 per minute.

The muscle record shows a brief initial rise, followed by a drop, and that in turn by another prolonged rise. The maximum height

of the record is 13.5 mm., an increase of 6 mm. over the height recorded before splanchnic stimulation. Thus the muscle was performing for a short period 80 per cent more work than before splanchnic stimulation, and for a considerably longer period exhibited an intermediate betterment of its efficiency.

1. The first rise in the muscle record. — The brief first elevation in the muscle record when registered simultaneously with blood pressure, is observed to occur at the same time with the sharp initial rise in the blood-pressure curve (see Fig. 3). The first sharp rise in blood pressure is due to contraction of the vessels in the splanchnic area, for it does not appear if the alimentary canal is removed, or if the coeliac axis and the superior and inferior mesenteric arteries are ligatured. The betterment of the muscular contraction is probably due directly to

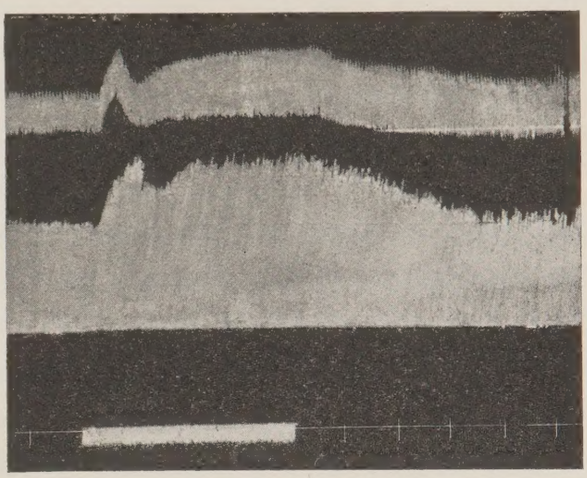


FIGURE 3. Top record, blood pressure with membrane manometer. Middle record, contractions of *tibialis anticus* loaded with 125 gm. and stimulated 80 times a minute. Bottom record, splanchnic stimulation (two minutes). Time, half minutes.

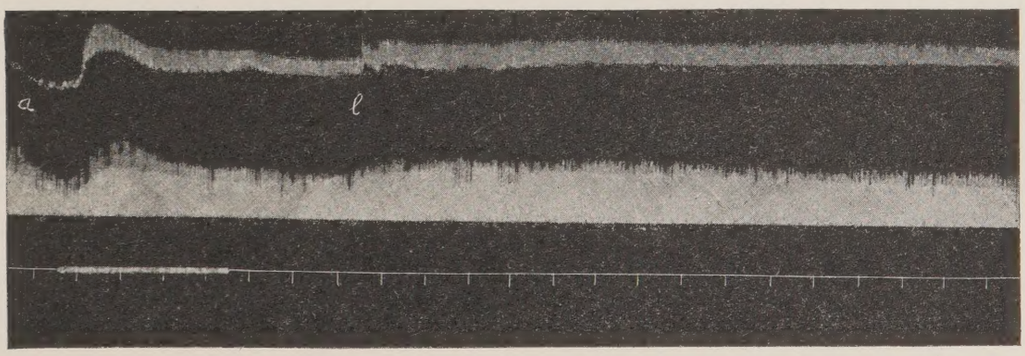


FIGURE 4. (Four-fifths the original size.) Top record, blood pressure with membrane manometer. Middle record, contractions of *tibialis anticus* against a spring. Bottom record, stimulation of left splanchnics. At *a* both adrenal veins were clipped, at *b* the clips were removed.

the better blood supply resulting from the increased pressure, for if the adrenal veins are clipped, and the splanchnic nerves are stimulated, the blood pressure rises as before and at the same time there may be registered a higher contraction of the muscle (see Fig. 4).

2. The prolonged rise of the muscle record. — As Fig. 3 shows, the initial quick uplift in the blood-pressure record is quickly checked by a drop. This rapid drop does not appear in Fig. 4, a record made when the adrenal veins were obstructed. The difference between Figs. 3 and 4 in this respect agrees with Elliott's observation of a similar difference in blood-pressure records before and after excision of the adrenal glands. And as Elliott,[8] and as Cannon and Lyman [9] have shown, this sharp drop after the first rise, and also the subsequent elevation of blood pressure, are the consequences of liberation of adrenal secretion into the circulation. Fig. 3 demonstrates that the prolonged rise of the muscle record begins soon after this characteristic drop in blood pressure.

In Fig. 4 removal of the clips from the adrenal veins after the splanchnics had been stimulated occasioned a slight, but distinct improvement in the muscular contraction. As in the experiments of Young and Lehmann, in which the adrenal veins were tied for a time and then released, the release of the blood which had been pent in these veins was quickly followed by a rise of blood pressure.[10] The volume of blood thus restored to circulation was too slight to account for the rise of pressure. In conjunction with the evidence that splanchnic stimulation calls forth adrenal secretion,[11] the rise may reasonably be attributed to that secretion. The fact should be noted, however, that in this instance the prolonged improvement in muscular contraction did not appear until the adrenal secretion had been admitted to the general circulation.

Figs. 2 and 3, and Fig. 4 illustrate two types of improvement in the activity of fatigued muscle in response to adrenal secretion. Many variations on these types were noted in the course of the investigation. The improvement varied in degree as indicated by increased height of the record. In some instances the height of contraction was doubled — a betterment by 100 per cent; in other instances the contraction after splanchnic stimulation was only a small fraction higher than that preceding the stimulation; and in still other instances there

[8] Elliott: Journal of physiology, 1912, xliv, p. 403.

[9] Cannon and Lyman: this Journal, 1913, xxxi, p. 376.

[10] Young and Lehmann: Journal of physiology, 1908, xxxvii, p. liv.

[11] *See* Asher: Zeitschrift für Biologie, 1912, lviii, p. 303; Elliott: Journal of physiology, *Loc. cit.*, p. 399.

was no betterment whatever. Never in our experience, were the augmented contractions equal to the original contractions of the fresh muscle.

The improvement also varied in degree as indicated by persistence of effect. In some instances the muscle returned to its former working level within four or five minutes after splanchnic stimulation ceased (see Fig. 2); in other cases the muscle continued working with greater efficiency for fifteen or twenty minutes after the stimulation.[12]

The question now arises, does the adrenalin liberated by splanchnic stimulation act itself, specifically, to improve the muscular contraction, or does it produce the improvement by increasing the blood pressure and thereby increasing the blood flow through the laboring muscle?[13] And further, since splanchnic stimulation results in an augmentation of the sugar content of the blood,[14] might not the greater ability of the muscle be due to a greater supply of this source of muscular energy? And in the cases in which no improvement occurred what was the reason for the failure? All these questions must be considered.

The Cause of the Prolonged Rise in the Muscle Record

The association of the first rise in the muscle record with an increase of blood pressure shows that the factor of blood supply is capable in itself of restoring to some degree the efficiency of a fatigued muscle

[12] "Tonus waves," similar to those described by Storey (this Journal, 1904, xii, p. 83), have been repeatedly observed by us. They had interesting relations to the discharge of adrenalin into the blood. If the waves were not present, splanchnic stimulation would often cause an augmented contraction in which the waves were present. Or if the waves were already present, splanchnic stimulation would commonly result in their being more rapid (see Fig. 6, *A* and *B*, also Fig. 7).

[13] It is assumed in this enquiry that vessels supplying active muscles would be actively dilated (*See* Kaufmann: Archives de physiologie, 1892, xxiv, p. 283), and would, therefore, in case of a general increase of blood pressure, deliver a larger volume of blood to the area they supply.

[14] MacLeod: this Journal, 1907, xix, p. 405, also for other references to the literature.

In order to differentiate between a possible specific action of adrenal secretion as an antidote to fatigue, and the effect which the secretion would have by increasing blood pressure, various methods were employed to keep the blood pressure constant during stimulation of the splanchnic nerves. Bayliss's compensator [15] proved too slow to be effective. The pressure was maintained at a uniform level in some

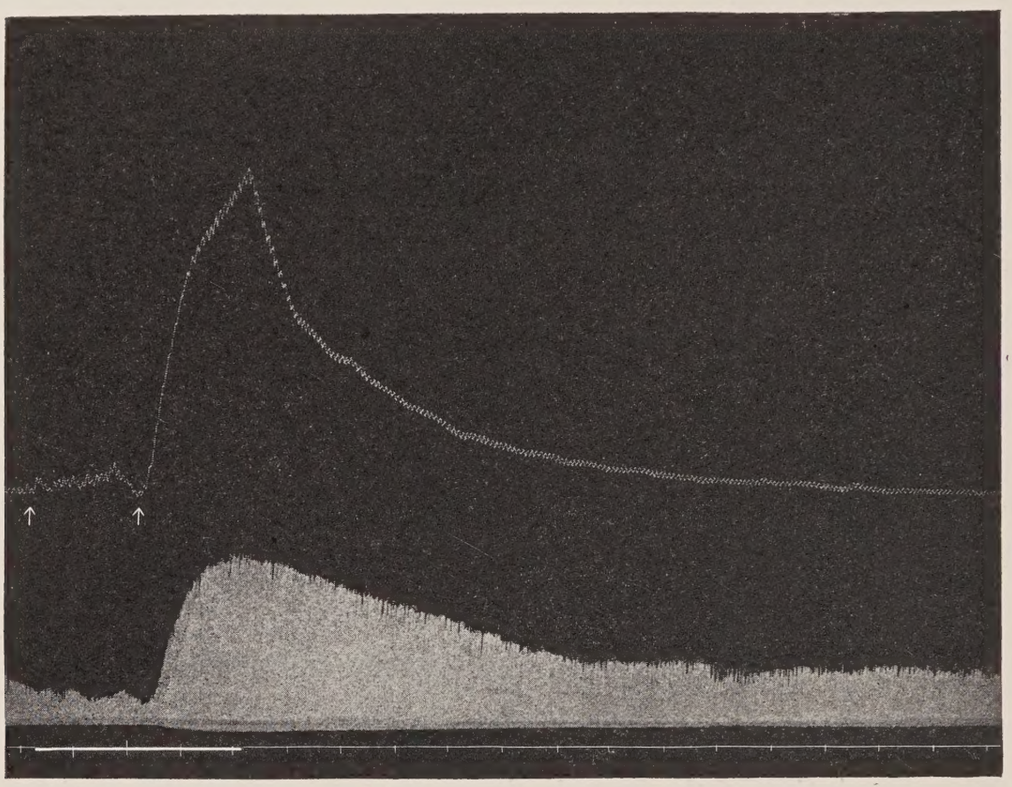


FIGURE 5. Top record, blood pressure with mercury manometer; between the arrows the pressure was kept from rising by compression of heart. Middle record, contractions of *tibialis anticus*, 180 per minute, against a spring. Bottom record (zero of blood pressure) shows stimulation of left splanchnics. Time, half minutes.

instances, however, by compression of the heart through the walls of the thorax. In other instances a loop of strong thread was passed through a small opening in the belly wall and around the abdominal aorta just before its forking into the iliacs. By more or less tension on the thread the pressure in the arteries of the legs could be regulated at will. This pressure was registered by means of a manometer attached to the left femoral artery. As soon as the pressure showed a

[15] *See* BAYLISS: Handbuch der physiologischen Methodik, 1911, ii, Abtheilung iv, p. 372.

tendency to rise the loop was pulled upon, and the inflow to the arteries of the leg thereby kept from increasing; as a tendency to fall manifested itself the pull on the loop was lessened.

The rôle of increased blood pressure when adrenal secretion is liberated. — In Fig. 5 is presented the record (from a decerebrate cat) of a fatigued muscle contracting 180 times per minute, and reduced to a very low degree of activity when splanchnic stimulation was started. The stimulation was continued for two minutes. During the first minute blood pressure was prevented from rising by compression of the heart, and in that time no betterment of the contraction appeared. As soon as compression of the heart ceased, however, the blood pressure promptly rose from approximately 48 mm. of mercury to 110 mm., and simultaneously the height of the muscular contraction increased about six-fold.

It is noteworthy that although the blood pressure gradually fell to its former level the muscle did not return to its former inefficiency. Merely because the blood supply *had been* better, probably because depressive metabolites had been thus washed away more effectively, and possibly because fresh sources of energy had been brought to the muscle in larger amount, the muscle continued to show a greater ability.

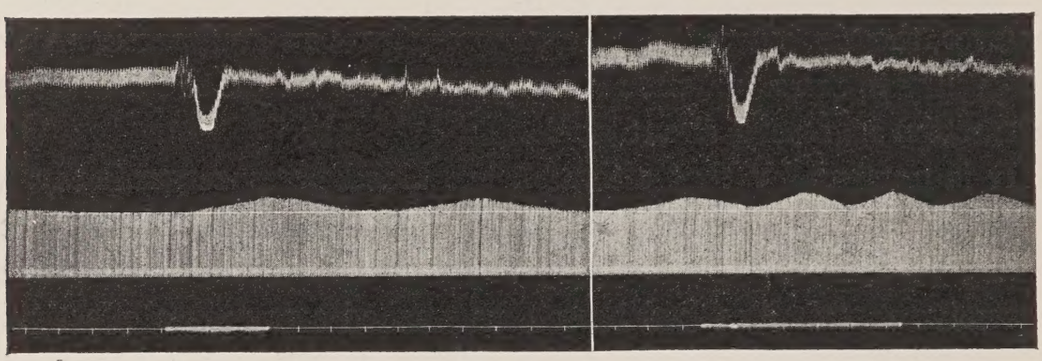
When the blood pressure was restored to its former level, the splanchnic nerves were again stimulated — this time for one minute. The blood pressure was kept down in this instance for one and three-fourths minutes by compression of the heart. Only slight tendency to higher contractions was manifested by the muscle during this period. And again only when the heart was permitted to fill and empty in a normal manner, and the pressure consequently rose, was there a considerable betterment of the contraction.

In these instances splanchnic stimulation undoubtedly liberated adrenalin, for the blood pressure remained elevated for fully seven minutes after the first stimulation ceased — a much longer time than is required for the adjustment of the circulation after compression of the thorax, but a time corresponding to the duration of effects of adrenal secretion. In spite of this the height of the muscle record failed to increase in any remarkable degree so long as the blood pressure was prevented from rising. The adrenal secretion, if it improves the contraction of fatigued muscle in a specific manner,

seems to have in that respect an influence much less important than that which it exercises in bettering the blood supply.

Does adrenalin have any specific effect on muscular fatigue?—Although in the instance represented in Fig. 5, and in some other instances when blood pressure was prevented from rising, no clear evidence of remarkable recovery from fatigue was noted after splanchnic stimulation, we have been unable to prove that adrenalin is without any specific effect on fatigued muscle.

In Fig. 6 *A*, for example, a fatigue record of uniform height was changed to a rhythm of higher contractions when the splanchnics



A B

FIGURE 6. (Two-thirds the original size.) *A*, top record, blood pressure in left femoral artery with mercury manometer. Middle record, contractions of the *extensor communis* against a spring. Bottom record, stimulation of left splanchnics, and time in half minutes. *B*, the same, five minutes after *A*. From the beginning of splanchnic stimulation to the end of the record in *A* and *B*, rise of blood pressure prevented by pull on the aorta.

were stimulated and the blood pressure in the legs prevented from rising by a pull on the aorta. And in Fig. 6 *B*, taken five minutes after *A*, the slow rhythm of *A* was changed by stimulation of the splanchnics to a more rapid rhythm of slightly higher contractions. That adrenalin was secreted in these cases is shown by the fall of blood pressure shortly after stimulation of the splanchnics was begun. It is noteworthy that the first oscillation in *A* does not start with the beginning of stimulation, but is coincident with the first indication of the fall of pressure.

Similar results are obtained if, instead of arousing adrenal secretion, adrenalin is injected. In Fig. 7, 2 c.c. of adrenalin (1 : 100,000) were injected intravenously during the period indicated on the time line. The blood pressure was prevented from rising by pulling on

the thread looped round the aorta. There was a typical fall of pressure after the injection. Accompanying it was a distinct increase in the height of the muscular contractions. Changes in blood pressure in the legs almost exactly the same as those following the injection of adrenalin could be produced by pulling on the aorta, but there resulted no alteration in the height of the fatigue record. The rise in that record shown in Fig. 7, therefore, is not due to diminished blood supply.[16] Also it is not due, therefore, to the introduction of sodium bicarbonate from the manometer connection into the circulation.

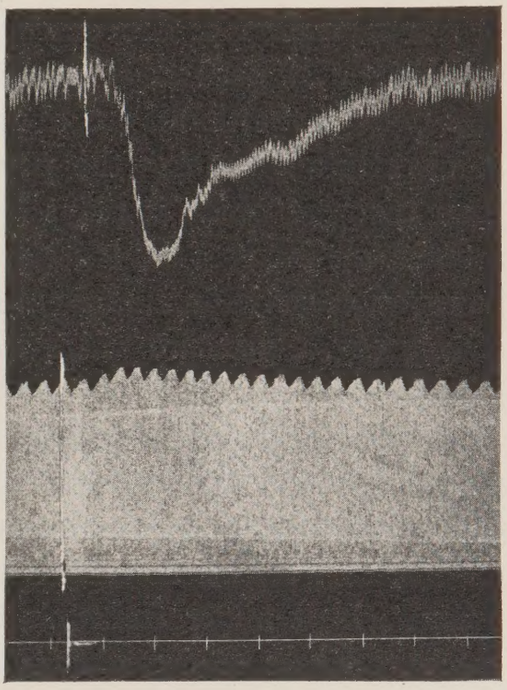


FIGURE 7. Top record, blood pressure, mercury manometer. Middle record, contractions of *tibialis anticus*, 180 times per minute, against a spring. Bottom record, injection of 2 c.c. adrenalin (1: 100,000), and time in half minutes. Rise of blood pressure prevented by pull on the aorta.

The drop in blood pressure following injection of adrenalin, or as a consequence of adrenal secretion, is due to vasodilation.[17] It might be supposed that, because of vasodilation, and in spite of a general fall of pressure, the blood supply to the muscle would be improved; and therefore, even in the case represented in Figs. 6 and 7, the higher contraction should be ascribed to better circulation. Against this supposition is the observation that when the arteries are deprived of their central innervation, as was the case with the arteries supplying the contracting muscle, adrenalin causes not a dilation but a constriction of the vessels.[18] And even if adrenalin did not cause vasoconstriction in this region, it could hardly produce much further dilation, for, as already noted, the vascular nerves had been cut and furthermore

[16] LEE'S suggestion (this Journal, 1907, xviii, p. 272) that increase of carbon dioxide increases the height of muscular contraction makes the effect of lessened blood supply worthy of consideration.

[17] *See* CANNON and LYMAN: *Loc. cit.*, p. 384.

[18] *See* CANNON and LYMAN: *Loc. cit.*, p. 387.

were being stimulated at a rate favorable to relaxation (see p. 47). It seems probable, therefore, that adrenalin can itself act specifically in a manner not yet explained, to improve the contraction of fatigued muscle. This conclusion is in harmony with the observation of Dessy and Grandis, previously cited, that adrenal extract betters contraction when added to a solution in which the muscle is submerged.[19]

Consideration of the cases in which no improvement was observed. — Comparison of the records reproduced in Fig. 5 and in Fig. 7 shows that in all probability the part played by adrenalin itself in directly augmenting the power of fatigued muscle is much less than the part which it plays by improving the blood supply. The astonishing increase in the power of the muscle shown in Fig. 5, however, occurred in an animal with a blood pressure of only 48 mm. of mercury, a pressure which was more than doubled by splanchnic stimulation.

In the early experiments of this investigation the sole object of recording blood pressure was to note the relations between changes of pressure and the variations in muscular contraction, or the results on muscular contraction when the adrenals were stimulated and the pressure kept under control. In these early experiments, unfortunately, because of the reasons just given, the actual height of the blood pressure was not recorded.

The marked improvement of muscular contraction in some instances and the slight improvement or lack of improvement in others (*cf.* Figs. 2 and 7) in which the conditions seemed the same, led to an enquiry regarding the occasion for the difference. The fact soon appeared that although the slight improvement which we have attributed to adrenalin directly (see Fig. 7) can be manifested even if the blood pressure is as high as 140 or 150 mm. of mercury, such improvement as is shown in Figs. 3 and 5 does not appear unless there is a low blood pressure. And if the pressure is down as low as 50 mm. of mercury, splanchnic stimulation or injection of a small dose of adrenalin will cause the pressure to increase greatly, and a striking betterment of muscular work results.[20] The effects of adrenal

[19] We have been unable to confirm this observation by similar use of frog muscles.

[20] The exact relations between variations of blood pressure and muscular efficiency are now being investigated in this laboratory by Mr. C. M. Gruber.

secretion, therefore, seem to be of two sorts; (1) a direct specific effect which benefits a fatigued muscle even when blood pressure is high, and (2) an indirect effect due to better circulation, and (within limits which are as yet undetermined) more striking the lower the blood pressure.

Elimination of hyperglycaemia as a cause of the higher contraction. — In the course of these experiments we repeatedly found sugar in the urine — a result probably due to hyperglycaemia from splanchnic stimulation. Recently Wilenko[21] has declared that the ability of the organism to burn sugar is lessened by adrenalin. It may be, however, that because of the artificial conditions of his experiments, their pertinence, when applied to the natural hyperglycaemia and adrenalinaemia of splanchnic origin, is questionable. Whether the adrenal secretion liberated with sugar when the splanchnics are stimulated does or does not similarly check the utilization of the sugar, data are at hand to prove that the hyperglycaemia is not essential to improved muscular contraction as described above. The sugar which makes the hyperglycaemia following splanchnic stimulation comes from the liver. The liver can be almost wholly removed, without disturbing the blood flow in the inferior vena cava, and yet splanchnic stimulation causes the typical rise in the muscle curve.

Discussion of Results

It is noteworthy that the best results of adrenalin on fatigued muscle reported by previous observers were obtained from studies on cold-blooded animals. In these animals the circulation is maintained normally by an arterial pressure about one-third that of warm-blooded animals. Injection of adrenalin in an amount which would not shut off the blood supply would, by greatly raising the arterial pressure, markedly increase the circulation of blood in the active muscle. In short the conditions in cold-blooded animals are quite like those in the pithed mammal with an arterial pressure of about 50 mm. of mercury (see Fig. 5). Under these conditions the improved circulation causes a striking recovery from fatigue. That marked results

[21] Wilenko: Biochemische Zeitschrift, 1912, xlii, p. 49; Zentralblatt für Physiologie, 1913, xxvi, p. 1059.

of adrenalin on fatigue are observed in warm-blooded animals only when they are deeply anaesthetized or are deprived of the medulla, was claimed by Panella. He apparently believed that in normal mammalian conditions adrenalin has little effect because quickly destroyed, whereas in the cold-blooded animals, and in mammals whose respiratory, circulatory and thermogenic states are made similar to the cold-blooded by anaesthesia or pithing, the contrary is true.[22] In accordance with our observations on the effects of blood pressure on fatigued muscle, we would explain Panella's results not as he has done but as due to two factors. First, the efficiency of the muscle, when blood pressure is low, follows the ups and downs of the pressure much more directly than when the pressure is high (see p. 56). And second, a given dose of adrenalin raises a low blood pressure in atonic vessels, whereas it may lower the pressure or fail to cause a marked rise in vessels tonically contracted. The improvement of circulation is capable of explaining, therefore, the main results obtained in cold-blooded animals and in pithed mammals.

Oliver and Schäfer reported more effective contractions in muscles removed from the body after adrenal extract had been injected. As shown in Fig. 5, however, the fact that the circulation *had been* improved results in continued greater efficiency of the contracting muscle. Oliver and Schäfer's observation may reasonably be accounted for on this basis.

How the improvement in muscular contraction, after adrenal secretion is evoked or after adrenalin is injected, can be explained, is not clear. The results above reported show that the improvement, though not great, is distinct, and that it apparently does not result from better circulation. According to Panella[23] adrenalin has an effect antidotal to curare, and, injected either mixed with or following curare, is capable of preventing the complete immobility which the curare alone would produce. This experiment points to an action of adrenalin in the region of transfer of influence from the nerve to the muscle. Radwánska[24] also reported finding that adrenalin has a more favorable action on fatigued muscle if the muscle is being stimulated through its nerve than if stimulated directly, and

[22] Panella: *Loc. cit.*, p. 462.

[23] Panella: Archives italiennes de biologie, 1907, xlvii, p. 30.

[24] Radwánska: *Loc. cit.*

he drew the inference that its beneficial effect is on the nerve endings. It seems quite possible therefore that the improved contraction of fatigued muscle after splanchnic stimulation, when rise of arterial pressure is prevented, is the consequence of a facilitation of the passage of impulses into the fatigued muscle.

The original purpose of this investigation was to learn whether the increased adrenal secretion accompanying major emotional states and pain [25] might act as a dynamogenic factor in the performance of muscular work. Apart from the increase of arterial pressure in conditions of low pressure, the change wrought by adrenal secretion on the efficiency of muscle is too slight to account for the feats of strength which are performed in times of great excitement. The main source of power under these conditions is probably to be found in an immensely augmented activity of the nervous system. The observations here recorded, however, indicate that adrenalin may operate favorably in making more effective the nervous impulses delivered to fatigued muscles.

Summary

If the *tibialis anticus* muscle, stimulated through its isolated nerve, is writing a fatigue curve, excitation of the left splanchnic nerves, also isolated, usually produces an increased height of contraction in the muscle record. (See Figs. 2 and 3.) Since splanchnic stimulation discharges adrenal secretion, the question is raised as to the effect of adrenal secretion on skeletal muscle.

The betterment of action of the fatigued muscle is mainly due to the increased blood flow resulting from splanchnic stimulation, and is more marked the lower the blood pressure when the splanchnics are excited. (See Fig. 5.) The betterment of the muscular contraction may long outlast the change in the circulation. Probably most previously reported effects of adrenalin on skeletal muscle (observed in cold-blooded animals with low blood pressure) should be attributed to the change in circulation and not to a specific action of adrenalin.

If, by pull on the aorta or by compression of the thorax, blood

[25] *See* Cannon and de la Paz: this Journal, 1911, xxviii, p. 64; Cannon and Hoskins: this Journal, 1911, xxix, p. 274.

pressure in the hind legs is prevented from rising, splanchnic stimulation still causes a slight but distinct rise in the height of contraction of the fatigued muscle. This betterment may appear in rhythm or altered rhythm. (See Fig. 6.) Its initial appearance coincides with evidence of adrenal secretion. It is produced also when adrenalin in weak solution (1 : 100,000) is given intravenously. (See Fig. 7.)

The improvement of muscular contraction which apparently results from adrenal secretion (when the blood pressure is controlled) is too slight to account for the increased muscular power observed during excitement. Fatigued muscles may, however, be thus prepared, by secretion of the adrenal glands, for better response to the demands of powerful nervous discharges.

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